larly pleased with the prospect of primary physicians having to weigh their own economic well-being directly against their patients' needs. But the primary care dilemma is that by not "squeezing the primaries," to use the jargon of the insurance industry, it is difficult (if not impossible) to restrain overall spending. A credible way out of this dilemma will do much to preserve the compact of trust between American physicians and their patients.

Book Review

The Western Journal of Medicine does not review all books sent by publishers, although information about new books received is printed elsewhere in the journal as space permits. Prices quoted are those given by the publishers.

The Consequences of Chromosome Imbalance—Principles, Mechanisms and Models

Charles J. Epstein, MD, Professor of Pediatrics and Biochemistry, University of California, San Francisco. Cambridge University Press, 32 E 57th St, New York, NY 10022, 1986. 475 pages, $59.50.

Charles Epstein has written a scholarly book about the chromosomes. The clinician who needs a catalog to help him or her put together the various pieces of a syndrome represented by a patient in a way that suggests a specific cytogenetic diagnosis or at least leads him or her to order a karyotype will find today many catalogues of cytogenetic diseases. This book is different. It represents a concerted attempt to understand, as thoroughly as data available today will permit, the ways in which chromosomal imbalance produces very highly specific phenotypes of abnormalities.

The organization of the book is interesting. The initial consideration is of the diversity of clinical phenotypic expression of autosomal aneuploidy, with an emphasis on what in the way of general principle can be gleaned from this analysis of clinical experience. The book proceeds to a theoretical approach to the mechanisms by which aneuploidy produces its phenotypic effects and to experimental data bearing on this issue. The author then discusses in detail three prototypes of aneuploidy: trisomy 21, XO monosomy, and chromosomes and cancer.

It is becoming increasingly possible to map just which portions of a chromosome are responsible in aneuploidy for the phenotypic features that identify a syndrome. Thus, the nuclear projections on polymorphonuclear leukocytes that are characteristic of trisomy 13 result from duplication of the very proximal part of the long arm of the chromosome, whereas the typical polydactyly is the result of extra material from the most distal portion. The situation in Down's syndrome is more closely delimited. The full phenotype is present when there is duplication of the area of chromosome 21 delimited by band 21q22. This is the area that contains the genes for the enzyme superoxide dismutase (SOD1), an enzyme that is thought to protect cells from oxygen-containing free radials and phosphoribosylglycinamide synthetase (PRGS), an enzyme of purine synthesis. Superoxide dismutase is the prototypical enzyme in which careful studies of enzyme activity indicated a gene dosage effect in trisomy 21. The activity in trisomic cells approximates 1.5 times that of normal diploid cells, and the SOD1 messenger RNA is increased to a similar degree. The same increase in enzyme activity in trisomic cells is true of PRGS and other enzymes that have been mapped to this area. Similarly, activity in monosomic cells has been found to approximate 0.5.

Despite these and other specific correlates of the state of trisomy for chromosome 21, it remains difficult to make the jump from any of the known associations to an acceptable pathogenetic mechanism for any of the striking phenotypic features such as mental retardation, immunodeficiency, or the propensity for malignancy. In each case the author has reviewed the extensive literature and its implications in detail and, with appropriate reservation, concluded that we have much more to learn before we can really understand the nature of the relationships.

A feature that has generated considerable recent speculation is the relationship of Down's syndrome to Alzheimer's disease. The brains of adults over 35 with Down's syndrome have histologic changes and neurofibrillary tangles that are indistinguishable from those of patients with Alzheimer's disease. A major component of these plaques is an amyloid beta-protein that is identical in both groups of patients. It may be a lead that since the review for this book was concluded in 1984 the gene for this beta-protein has been mapped to chromosome 21, and it is thought that familial Alzheimer's disease can also be traced to chromosome 21. Similarly, the recent mapping of an oncogene, the *ets*-2 gene, to the 21q22 region may provide the link to the pathogenesis of leukemia and other neoplastic diseases in patients with trisomy 21.

Some of the critical connections may be discovered now that an animal model has become available. This area, first explored by Gropp of Lübeck, has largely been developed by the author and his colleagues. Chromosome 16 in the mouse is homologous with human chromosome 21 with regard to the various loci that have been mapped, including SOD1, PRGS, and *ets*-2. Mice trisomic for chromosome 16 have a phenotype with many of the features of Down's syndrome, including an endocardial cushion defect. Better models may be mice that are trisomic for smaller parts of chromosome 16, and work is under way to produce such animals. Transgenic mice, products of modern recombinant DNA technology, in which single genes or groups of genes are transferred early in development, should permit the very fine dissection of interrelationships between phenotype and genotype.

The author is professor of pediatrics and biochemistry at the University of California, San Francisco. His book will be of greatest use to investigators working in the field. It will also be of interest to clinical geneticists, cytogeneticists, dysmorphologists, and others concerned with the understanding of chromosomal abnormalities. The powerful tools at hand for further investigation of this field promise that it is poised for a major series of advances. We shall look forward with interest to the next edition.

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